

## Lidocaine and Pentylenetetrazol Seizure Thresholds in Cats Are Not Reduced after Enflurane Anesthesia

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Some previous reports indicate that the excitability of the brain may be increased for days following enflurane anesthesia. The authors investigated this possibility in cats by determining whether or not pentylenetetrazol (Metrazol®) or lidocaine-seizure thresholds decreased after repeated enflurane exposure. The lidocaine-seizure threshold was bracketed in 4 cats, and the pentylenetetrazol-seizure threshold was bracketed in another 4 cats. Each cat was then exposed to 4 per cent enflurane for 2 hours on 4 successive days. Twenty-four hours after the last enflurane exposure, the cats were injected with the previously determined subthreshold dose of pentylenetetrazol (6.4 mg/kg, on the average) or lidocaine (7.8 mg/kg, on the average). No cat convulsed. It was therefore concluded that under our experimental conditions, repeated enflurane exposure does not increase the sensitivity to drugs which nonselectively excite the central nervous system (e.g., pentylenetetrazol) or to drugs which mimic temporal lobe epilepsy (e.g., lidocaine). This finding casts doubt that brain excitability is increased in the post-enflurane anesthetic period. (Key words: Anesthetics, local: lidocaine. Anesthetics, volatile: enflurane. Brain: convulsions; electroencephalography; seizure threshold. Complications: convulsions. Pharmacology: pentylenetetrazol.)

ENFLURANE PRODUCES EPILEPTIFORM ACTIVITY on the electroencephalogram (EEG) of humans and animals, even during relatively light levels of anesthesia.<sup>1,2</sup> Moreover, grand mal seizures can be precipitated by hyperventilating the enflurane-anesthetized patient.<sup>3†</sup> There is also evidence that enflurane's proconvulsant effect may extend into the postanesthetic period. High-voltage spike activity occurring at short intervals was observed in the cortex and in the thalamic nuclei of cats 2-16 days following enflurane anesthesia.<sup>4,5</sup> Furthermore, reports in the literature<sup>6,7</sup> suggest a possible link between enflurane anesthesia and postoperative seizures in 3 patients.

The objective of this study was to determine if brain excitability, as measured by responses to intravenously

injected lidocaine and pentylenetetrazol (PTZ), is increased by repeated enflurane exposure.

### Methods

Our experimental protocol consisted of determining the lidocaine- or PTZ-seizure threshold of cats, then anesthetizing each animal with enflurane for 2 hours on 4 consecutive days. On the day following the last enflurane anesthetic, each animal was injected with the previously determined just subconvulsant dose of PTZ or lidocaine to determine if seizure threshold for the drugs had fallen.

For the studies, 8 healthy, adult male and female cats were anesthetized with halothane and prepared for chronic EEG recording. Electrodes were placed bilaterally in the calvarium over the frontal (cruciate sulcus), midsylvian, and occipital regions of the cortex and an indifferent electrode was placed over the frontal sinus. Leads from the electrodes were soldered to a plug that was permanently bonded to the cat's skull. All cats quickly recovered on discontinuation of anesthesia and showed no signs of ill health or neurologic sequelae.

Spontaneous electrical activity from the brain was passed through a cable terminating in a mate to the skull plug, to an 8-channel polygraph (0.3-75 Hz bandpass) and a 7-channel FM tape recorder. In determining lidocaine- and PTZ-seizure thresholds, high-voltage epileptiform spike bursts on the EEG, appearing synchronously in all leads and alternating with electrically quiet periods, were considered indicative of generalized convulsions. These spike bursts were invariably accompanied by generalized tonic-clonic contractions of facial and limb muscles.

Lidocaine for injection (1 or 2 per cent solution) was made by dissolving lidocaine hydrochloride (Xylocaine®) crystals‡ in sterile saline solution and adjusting the pH of the solution to 6.9-7.0 with sodium hydroxide. Pentylenetetrazol was prepared for injection by diluting commercial§ 10 per cent solution tenfold with saline solution.

We began establishing seizure thresholds 2 weeks

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† Stockard JJ, et al: The effects of nitrous oxide and carbon dioxide on epileptiform EEG activity produced by enflurane. Annual meeting of the American Society of Anesthesiologists, 1975, pp 309-310.

‡ Courtesy Astra Pharmaceutical Products.

§ Metrazol®, Knoll Pharmaceutical Company, includes 0.1 per cent Na<sub>2</sub>PO<sub>4</sub>.

TABLE 1. Bracketing Doses (mg/kg) of Lidocaine and Pentylenetetrazol (IV)

	Cat	No Seizures	Seizure
Lidocaine	1	7.1	8.0
	2	7.1	8.0
	3	5.6	6.3
	4	11.2	12.6
Pentylenetetrazol	5	7.1	8.0
	6	5.0	5.6
	7	5.6	6.3
	8	8.0	8.9

or more after electrode implantation. Seizure thresholds were determined by injecting PTZ (5.0–10.0 mg/kg) or lidocaine (5.6–12.6 mg/kg) intravenously at a rate of  $1 \text{ mg} \cdot \text{kg} \cdot \text{s}^{-1}$ . Doses were increased or decreased in 0.05 log units at weekly or longer intervals to bracket the doses of lidocaine and PTZ that just produced and did not produce a seizure. Using this technique, the seizure threshold dose is defined as the geometric mean of the doses that just produced and did not produce a seizure.<sup>8</sup>

Beginning one to 14 days after the lidocaine- or PTZ-seizure threshold was established, the cats were anesthetized with enflurane for 2 hours on 4 consecutive days. Each day, anesthesia was administered to the cat by means of an infant circle absorber system equipped with an infant face mask. Oxygen served as the carrying and diluent gas. Percentages of inspired

enflurane were calculated using the Copper Kettle Calculator<sup>¶</sup> and confirmed by gas chromatography.

Induction with 7–8.5 per cent enflurane was followed by tracheal intubation under direct vision. No neuromuscular blocking agent, topical anesthetic spray, or lubricant was used. When intubation was completed, the animals were maintained on mechanical ventilation with 4 per cent enflurane. Initially, ventilation rate was set at 28 strokes/min and tidal volume was set to maintain carinal expired  $\text{CO}_2$  at 3.6–4.4 per cent.

On the first day of enflurane exposure, a chronic arterial cannula was placed in a femoral artery.<sup>9</sup> In most cases, the cannula remained patent for the next three days. Arterial pressure was measured and arterial samples were taken periodically for blood gas analysis. The day after the enflurane-exposure sequence ended, the cats were injected with a dose of lidocaine or pentylenetetrazol that just did not cause seizures before enflurane exposure.

## Results

### SEIZURE THRESHOLDS

All animals convulsed when injected with adequate doses of pentylenetetrazol or lidocaine. The seizure-bracketing doses of these two drugs are shown in table

¶ The Foregger Company, Inc.

### LIDOCAINE

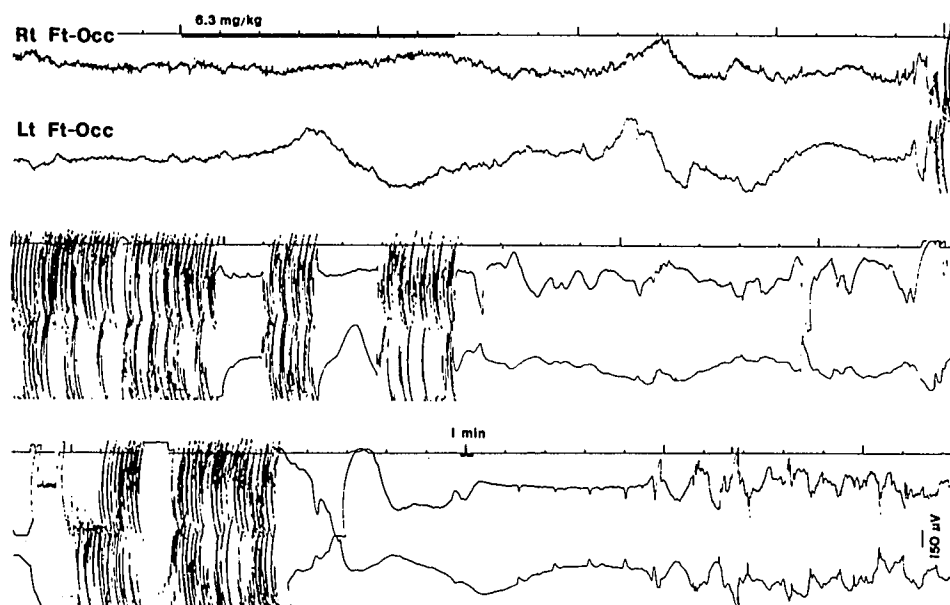
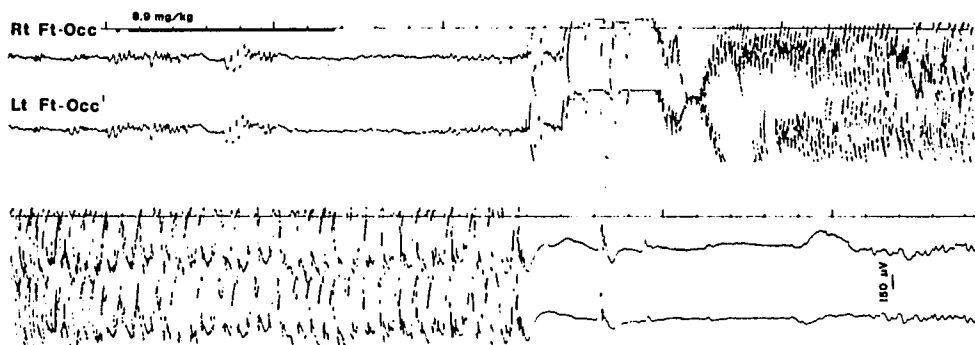


FIG. 1. Typical EEG pattern recorded during lidocaine-induced seizures. The trace is continuous from time of drug injection until after the seizure stopped. In this case, epileptiform activity stopped about one min after lidocaine injection and gave way to a diffuse, slow-wave EEG pattern. Right and left fronto-occipital recordings are shown. On this and subsequent EEG recordings, a time base with ticks at 1-s intervals is included.

# PENTYLENETETRAZOL

FIG. 2. Typical EEG pattern recorded during pentylenetetrazol-induced seizures. In this animal, epileptiform activity stopped about 40 s after drug injection and gave way to a high-frequency, low-amplitude EEG pattern. Right and left fronto-occipital traces are shown.



1. The average seizure-producing dose of lidocaine\*\* was  $8.2 \pm 2.6$  mg/kg. This agrees with a previously reported lidocaine median convulsant dose ( $CD_{50}$ ) of 8.4 mg/kg.<sup>8</sup> The average seizure-producing dose of PTZ was  $6.8 \pm 1.4$  mg/kg. Three to 7 injections of lidocaine or PTZ were required to bracket the seizure-threshold doses.

Usually, a PTZ seizure began and ended more abruptly than did a lidocaine-induced seizure. With both drugs, however, the EEG during seizures had typical epileptiform activity characterized by large amplitude potentials with fast rise and decay times, occurring in rapid succession (figs. 1 and 2).

\* Determined by averaging the geometric mean of the doses that just did and just did not produce a seizure.

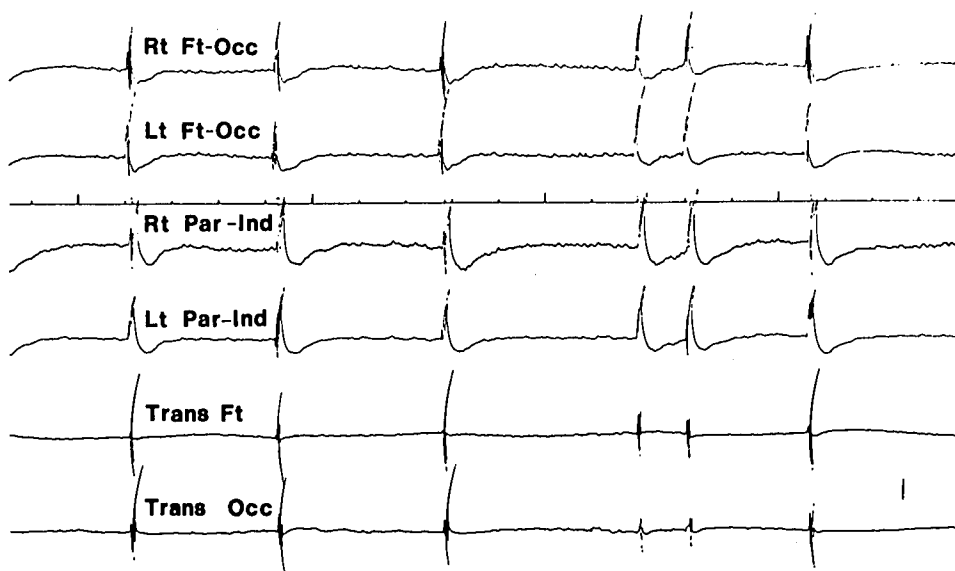
## ENFLURANE EXPOSURES

Mask induction with enflurane was rapid; however, tracheal intubation was consistently difficult because of active laryngeal reflexes and rapid awaking of the animal during intubation attempts. Central esophageal temperature ranged between 37° and 39° C during all enflurane exposures, and systolic blood pressure never fell below 80 torr.

During enflurane exposure, the EEG pattern corresponded to early or late level V<sup>1</sup> (fig. 3). This level is characterized by synchronous high-voltage EEG spiking separated by burst suppression periods of 3–10 s. Average intra-anesthetic arterial blood pH and  $P_{CO_2}$  values ( $7.36 \pm 0.04$  SD and  $29.6 \pm 6.6$  torr, respectively) were in the normal range for the cat.<sup>10</sup>

## ENFLURANE

FIG. 3. EEG level V<sup>1</sup> recorded after 120 min of enflurane anesthesia. Synchronous high-voltage EEG spiking is separated by burst suppression periods of 3 to 10 s. Rt = right; Lt = left; Occ = occipital; Ft = frontal; Par = parietal; Ind = indifferent. Vertical scale on lower right = 150  $\mu$ V for Ft-Occ traces, 100  $\mu$ V for Lt Par and Trans traces; and 75  $\mu$ V for Rt Par.



## AWAKE EEGS

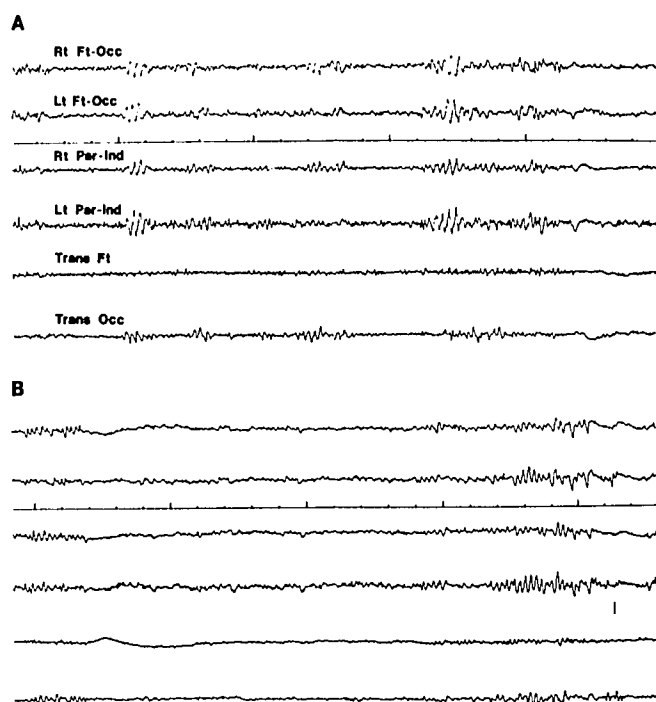


FIG. 4. Awake EEGs recorded from one cat on the first day of study (A) and just before the post-enflurane seizure challenge (B).

In no case were spontaneous behavioral signs of grand mal seizures observed between or during anesthetic sessions. Occasionally, facial twitching would accompany EEG spikes during anesthesia.

#### POST ENFLURANE LIDOCAINE/ PENTYLENETETRAZOL RESPONSES

After the enflurane exposures, no animals seized when injected with the previously determined subthreshold dose of lidocaine or PTZ. This indicates that repeated enflurane exposures increase the susceptibility to the proconvulsant effects of lidocaine or PTZ little if at all, or possibly even decrease the susceptibility. Our experimental approach would not detect a slight decrease in seizure threshold; we can only estimate the "seizure threshold" doses of lidocaine and PTZ and know that they are somewhere between the approximately 13 per cent difference between the doses that just did and just did not produce seizures. Likewise, the experiment was not designed to test for seizures threshold increases.

#### OTHER OBSERVATIONS

No behavioral or EEG changes suggestive of long lasting and/or cumulative effects of the enflurane

exposures were observed. All animals remained in good health and maintained their body weight throughout the study. Also, EEG patterns during enflurane exposure were similar each day and the awake EEG patterns recorded on the first day of study and just before the final seizure testing were similar (fig. 4). Animals promptly awakened upon termination of anesthetic and on the following day showed no evidence of change in behavior or level of consciousness. Moreover, behavioral and EEG changes induced by the subthreshold dose of lidocaine or PTZ were the same before and after the multiple enflurane exposures.

#### Discussion

These observations do not reveal an increased excitability of the brain after multiple enflurane exposures. We obviously cannot rule out the possibility that an excitability increase occurred that was not detectable with the resolution (less than 0.05 log units) of the seizure dose bracketing technique used. Our opinion is that such a small change, if it occurred, would be inconsequential in the development of spontaneous seizures in the postanesthetic period. In considering these results, however, one must bear in mind that the means by which lidocaine and PTZ induce seizures may not mimic the means by which spontaneous seizures develop, nor is it likely that these two agents cover the possible spectrum of means by which all proconvulsant chemicals induce seizures. Thus a similar study employing other means of testing brain excitability may yield different results.

There is also the possibility that slight modification of the experimental protocol might yield different results. For instance, decreasing or increasing the number of consecutive enflurane exposures, or not testing for seizure-threshold change until the second, third, etc., day after the last enflurane exposure might reveal a seizure-threshold change. In selecting the protocol used, we reasoned that if there was a seizure-threshold reduction due to metabolite accumulation, then multiple enflurane exposure might yield greater metabolite level than a single exposure. Likewise, we reasoned that if single enflurane exposures produce a subliminal seizure propensity, then multiple enflurane exposures might have a summing action similar to the "kindling phenomenon."<sup>11</sup> On the other hand, there is typically a time in the post-ictal period wherein the brain is refractory to seizure induction. It is possible that such refractoriness was present when we injected the post-enflurane challenge of PTZ or lidocaine. Similarly, it is possible

that some sort of "tolerance" developed during the seizure testing regime and/or during the enflurane exposure. This possibility cannot be totally discounted. However, our experience with lidocaine-seizure testing indicates that repeated lidocaine injections spaced at weekly intervals do not change lidocaine-seizure thresholds. We also did not see a progressive decrease or increase in epileptiform bursts on the EEG during the sequential enflurane exposures that would suggest development of tolerance (refractoriness) or an increased brain excitability, respectively.

Lidocaine and PTZ produce seizures in quite different fashions. Lidocaine apparently initiates grand mal seizures by exciting the limbic brain (amygdala and hippocampus, in particular).<sup>12</sup> Similarities between lidocaine-induced seizures and temporal-lobe epilepsy have been noted.<sup>13</sup> There is also evidence that the limbic brain and structures associated with the limbic system and its pathways are the epileptogenic foci of enflurane-induced seizures in the rat.<sup>14</sup> However, much evidence indicates that PTZ is a general CNS excitant,<sup>15</sup> although recent research demonstrates that it specifically causes a decrease in transmitter-evoked chloride conductance.<sup>16</sup>

One must also be cautious in extrapolating these animal data to humans. Among other factors to be considered in such extrapolation are possible differences in metabolism of enflurane, especially since it has been suggested that enflurane metabolites may be the cause of post-enflurane anesthesia CNS changes seen in humans.<sup>7,17</sup> Enflurane metabolism has been examined in human subjects but not in cats, thus a basis for correlating possible accumulation of metabolites is lacking.

The fact that we observed no changes in the behavior or awake EEG pattern of the cats after enflurane exposure contradicts what has been previously reported. For instance, Julien and Kavan<sup>4</sup> observed that 10 cats anesthetized with enflurane (5.5 per cent) for 30 min, exhibited marked behavioral changes by the second postanesthetic day. The animals resisted handling and appeared frightened. In addition, the behavioral changes were accompanied by high-voltage spike activity occurring at short intervals in the cortex and thalamic nuclei. These investigators also reported<sup>5</sup> postanesthetic effects in another group of cats anesthetized with enflurane for 30 min at a level that prevented withdrawal response to electrical stimulation of a paw. For 48 hours, the animals appeared frightened, walked close to walls and furniture with a staggering gait, and resisted handling. EEG changes as just described were also observed. The reason we did not see the EEG and behavioral changes

these other investigators reported is not readily apparent. Certainly our anesthetic conditions differed from those in the other studies, but one would expect our conditions to enhance any residual enflurane or enflurane metabolite-induced changes.

The fact that the other investigators implanted multiple electrodes in subcortical sites as opposed to no such electrodes in our animals, could be a reason for the different observations. It is possible that the presence of the depth electrodes caused local irritation which was augmented by enflurane or metabolites. It is also possible that during the course of the subcortical electrical implantation, blood vessels were ruptured, resulting in ischemic areas which produced local irritation that was augmented by enflurane or a metabolite. On the other hand, no depth electrodes were implanted in human volunteers who had prolonged EEG changes following enflurane anesthesia.<sup>12</sup> But the EEG changes seen in the cortical recordings from the humans were distinctly different from those seen in the cats; none of the human patterns consisted of sharp wave, epileptiform activity. In considering the human EEG data, Burchiel *et al.*<sup>7</sup> raised the possibility that in humans, there is a time after enflurane anesthesia during which certain deep brain structures have increased incidence of epileptiform activity. These investigators postulated that such activity may not be detected on conventional EEG recordings, nor be significant unless the patient has an established, epileptic focus or otherwise has an occult predisposition to epileptiform activity. Whether such is the case, and if so, whether it is unique to enflurane anesthesia, warrants further study. Certainly, our data show that in normal, healthy cats the brain's sensitivity to lidocaine- or pentylenetetrazol-induced seizures is not increased 24 hours after multiple enflurane anesthetics. In addition to the possible clinical significance relative to post-enflurane seizures in humans, the results suggest that lidocaine can be used in patients 24 hours following enflurane anesthesia without increased likelihood of manifestation of the CNS toxicity of this local anesthetic and antiarrhythmic drug.

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